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Applicant : Hanna et al.) Prior Group Art Unit 1615
Appl. No. : Unassigned) I hereby certify that this correspondence and all
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For : METHOD AND APPARATUS FOR) the United States Postal Service as Express Mail
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Prior Examiner : J. Strickland) Commissioner for Patents, P.O. Box 2327,
Arlington, VA 22202, on

November 27, 2001

(Date)

Kathy Honnert
Kathy Honnert

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Dear Sir:

Entry and consideration of the present Preliminary Amendment are requested prior to examination of the above-identified application on its merits.

IN THE SPECIFICATION:

On page 1, line 4, please insert after the following new paragraph:

This application is a continuation of U.S. Patent Application Serial No. 09/379,549, filed August 23, 1999, which is a continuation of U.S. Patent Application Serial No. 08/765,540, filed February 19, 1997, now Patent No. 6,063,138, which corresponds to the U.S. national phase filing under 35 U.S.C. §371 of PCT application No. PCT/GB95/001523, filed June 30, 1995, which claims priority to UK Patent Application No. 9413202.4, filed June 30, 1994.

IN THE CLAIMS

The claims under consideration are not the claims as originally filed in the International application, but rather amended claims 1-29. Please cancel claims 1- 29, and add the following new claims:

30. Apparatus for use in the formation of a particulate product, comprising:
a particle formation vessel;
a mechanism for controlling the temperature in said vessel;
a mechanism for controlling the pressure in said vessel; and
an inlet for the co-introduction into the vessel of a supercritical fluid and at least one substance in a vehicle, the inlet comprising a first passage for introduction of the supercritical fluid and a second passage for introduction of the substance, the first and second passages and their respective outlets being arranged relative to one another such that in use, supercritical fluid introduced through the first passage and the substance introduced through the second passage both enter the particle formation vessel at the same location and such that the flow of supercritical fluid can act to disperse the substance at the location where the fluids meet and enter the particle formation vessel.
31. Apparatus according to claim 30, additionally comprising a mechanism for the collection and/or retention of the particulate product in the particle formation vessel.
32. Apparatus according to claim 30 additionally comprising a mechanism for recovering the supercritical solution, formed on extraction of the vehicle into the supercritical fluid, from the particle formation vessel; a mechanism for separating the components of the supercritical solution; and optionally a mechanism for recycling one or more of said components back into the apparatus.
33. Apparatus according to claim 30, comprising more than one particle formation vessel and more than one mechanism for the collection of the particulate product either in the particle formation vessel or downstream therefrom, to allow for substantially continuous

operation of the apparatus through switching from one particle formation vessel or collection mechanism to another as required.

34. Apparatus according to claim 30, wherein at least the particle formation vessel may be substantially completely sealed from the external environment during use of the apparatus.

35. Apparatus according to claim 30, wherein the mechanism for the co-introduction of a supercritical fluid and a vehicle into the particle formation vessel allows them to be introduced with concurrent directions of flow.

36. Apparatus according to claim 35, wherein the mechanism for the co-introduction of the supercritical fluid and the vehicle comprises a coaxial nozzle, the outer end of which communicates with the interior of the vessel, the nozzle having coaxial passages which terminate adjacent to one another at the outlet end, at least one of the passages serving to carry a flow of the supercritical fluid, and at least one of the passages serving to carry a flow of the vehicle in which the substance is dissolved or suspended.

37. Apparatus according to claim 36, wherein the nozzle has two coaxial passages, an inner and an outer.

38. Apparatus according to claim 36, wherein the nozzle has three coaxial passages, an inner, an intermediate and an outer.

39. Apparatus according to claims 36, wherein the opening at the outlet end of the nozzle has a diameter in the range of 0.05 to 2 mm.

40. Apparatus according to claim 36, wherein the angle of taper at the outlet end of the nozzle is approximately 30°.

41. Apparatus according to claim 37, wherein the ratio of the internal diameters of the outer and the inner passages is between about 3 and 5.

42. Apparatus according to claim 38, wherein the ratio of the internal diameters of the outer and intermediate passages is between about 1.4 and 1.8.

43. Apparatus according to claim 31, wherein the mechanism for controlling the temperature in the particle formation vessel comprises an oven.

44. Apparatus according to claim 30, wherein the mechanism for controlling the pressure in the particle formation vessel comprises a back-pressure regulator.

45. Method for the formation of a particulate product comprising:
co-introducing through respective inlet passages a supercritical fluid and a vehicle containing at least one substance into a particle formation vessel, wherein the flows of the supercritical fluid and the vehicle containing the substance both enter the vessel from said passages at the same location which is substantially the same as the location at which they meet, the inlet passages are further arranged such that the flow of supercritical fluid is used to disperse the vehicle containing the substance and that the supercritical fluid can simultaneously extract the vehicle from the substance at the location where the fluids meet.

46. Method according to claim 45 further comprising controlling the temperature and pressure within the particle formation vessel.

47. Method according to claim 45, wherein the co-introduction of the supercritical fluid and the vehicle is effected using a coaxial nozzle the outlet end of which communicates with the interior of the particle formation vessel, the nozzle having coaxial passages which terminate adjacent to one another at the outlet end, at least one of the passages serving to carry a flow of the supercritical fluid, and at least one of the passages serving to carry a flow of the vehicle.

48. Method according to claim 45 wherein the substance is in solution in the vehicle.
49. Method according to claim 45 wherein the substance is suspended in the vehicle.
50. Method according to claim 45, wherein the supercritical fluid is carbon dioxide.
51. Method according to claim 45, wherein the supercritical fluid contains one or more modifiers.
52. Method according to claims 45, wherein the product to be formed is a pharmaceutical compound.
53. Method according to claims 45, additionally comprising the controlling the flow rate of the supercritical fluid and the vehicle; the concentration of the substance(s) in the vehicle; and the temperature and pressure inside the particle formation vessel.
54. Method according to claims 45, wherein the pressure in the particle formation vessel is maintained substantially in excess of the critical pressure for the supercritical fluid, whilst the temperature in the vessel is maintained at slightly above the critical temperature for the supercritical fluid.
55. Method according to claim 45, wherein the ratio of the vehicle flow rate to the supercritical fluid flow rate is between 0.001 and 0.1.
56. Method according to claim 45, additionally comprising the step of recovering and recycling the vehicle and the supercritical fluid following particle formation.
57. A method for forming particulates comprising a substrate surrounded by a coating layer comprising:

contacting a coating material and a substrate with a supercritical fluid upon co-introduction into a particle formation vessel.

58. A method according to claim 57 wherein said coating material is provided as a solution or suspension in a first vehicle.

59. A method according to claim 58 wherein said substrate is provided as a dispersion in a second vehicle.

60. A method according to claim 59 wherein the coating material is in solution.

61. A method according to claim 59 wherein the coating material is suspended in the first vehicle.

62. A method according to claim 59 wherein the first and second vehicles are provided separately to the particle formation vessel.

63. A method according to claim 59 wherein the co-introduction is such that the flow of supercritical fluid can simultaneously extract the first and second vehicles.

64. Method according to claim 63, wherein the co-introduction is effected using a coaxial nozzle the outlet end of which communicates with the interior of the particle formation vessel, the nozzle having coaxial passages which terminate adjacent to one another at the outlet end, at least one of the passages serving to carry a flow of the supercritical fluid.

65. A method according to claim 59, wherein the supercritical fluid, the solution or suspension and the second vehicle are co-introduced into the particle formation vessel by a nozzle having an outlet end communicating with the interior of the particle formation vessel, and two or more coaxial passages which terminate adjacent or substantially adjacent to one another at the outlet end, at least one of the passages serving to introduce

a flow of the supercritical fluid into the particle formation vessel, at least one of the passages serving to introduce a flow of the solution or suspension of the substance in the first vehicle and at least one of the passages serving to introduce a flow of the second vehicle.

66. A method according to claim 65, wherein the solution or suspension of the substance in the first vehicle is introduced into the particle formation vessel through one passage of the nozzle, and the supercritical fluid and the second vehicle are introduced together through another passage of the nozzle, and mixing of the two vehicles occurs substantially simultaneously with their dispersion and extraction by the supercritical fluid.

67. A method according to claim 66, wherein the nozzle has at least three coaxial passages, the solution or suspension being introduced between an inner and an outer flow of the supercritical fluid/second vehicle mixture.

68. A method according to claim 65, wherein the nozzle has at least three coaxial passages, the outlet of at least one of the inner nozzle passages being located a small distance upstream of the outlet of one of its surrounding passages, the distance being sufficient to allow a degree of pre-mixing to occur between fluids introduced through said inner and surrounding passages, and wherein the solution or suspension and the second vehicle are introduced through the inner passage and surrounding passage in question so as to allow, in use, a degree of mixing to occur, between the solution or suspension and the second vehicle, within the nozzle.

69. A method according to claim 68, wherein the nozzle has at least four coaxial passages, and wherein the solution or suspension and the second vehicle are introduced into the particle formation vessel between an inner and an outer flow of the supercritical fluid.

70. A method according to claim 63 wherein the temperature and pressure within the particle formation vessel are controlled.

71. A method according to claim 70, wherein the pressure in the particle formation vessel is maintained substantially in excess of the critical pressure for the supercritical fluid, whilst the temperature in the vessel is maintained at slightly above the critical temperature for the supercritical fluid.

72. A method according to claim 59 wherein said substrate comprises a pharmaceutically active agent.

73. A method according to claim 59 wherein said substrate comprises a pharmaceutically acceptable carrier.

74. A method according to claim 73 wherein said coating material comprises a pharmaceutically active agent.

75. A method according to claim 72 wherein said coating material comprises a pharmaceutically acceptable carrier.

76. A method according to claim 75 wherein said carrier comprises a taste-masking agent.

77. Method according to claim 57, wherein the supercritical fluid is carbon dioxide.

78. Method according to claim 57, wherein the supercritical fluid contains one or more modifiers.

79. Method according to claim 58, additionally comprising the control of the concentration of the substance(s) in the vehicle.

80. A method according to claim 59, wherein a flow rate of the second vehicle into the particle formation vessel is greater than that of the solution or suspension.
81. A method according to claim 80, wherein the ratio of the solution/suspension flow rate, into the particle formation vessel, to that of the supercritical fluid is between 0.001 and 0.2.
82. A method according to claim 59, wherein the amount of the first vehicle used is less than or equal to about 30% of the total amount of the first and second vehicles used.
83. A method according to claim 59, wherein one of the two vehicles contains functional groups that may interact, through hydrogen-bonding or dipole-dipole interactions, with functional groups contained in the other vehicle.
84. A method according to claim 59, wherein the substance and the first vehicle are substantially polar and the second vehicle is substantially non-polar.
85. A method according to claim 59, wherein the substance and the first vehicle are substantially non-polar and the second vehicle is substantially polar.
86. A method according to claim 59 wherein the substance is substantially insoluble in the second vehicle.
87. A method in accordance to claim 59, wherein the second vehicle contains a crystallization seed of a material which is insoluble in the second vehicle to induce nucleation of the substance when the second vehicle comes into contact with the solution or suspension of the substance in the first vehicle.
88. A method in accordance to claim 87, wherein the substance is a pharmaceutical substance, and the seed comprises a pharmaceutically acceptable carrier for the substance.

89. A method according to claim 57, which is carried out in a plural batch manner by switching between two or more particle formation vessels or between two or more means for collecting the particulate product.

90. A method for forming particulates comprising a substrate surrounded by a coating layer comprising:

contacting a first vehicle containing a coating material and a second vehicle containing a substrate with a supercritical fluid.

91. A method according to claim 90 wherein the contacting step comprises co-introduction of the first vehicle, second vehicle, and supercritical fluid into a particle formation vessel.

92. A method according to claim 91 wherein the first and second vehicles and supercritical fluid are co-introduced such that the flow of supercritical fluid can simultaneously extract the first and second vehicles.

93. A method according to claim 91 wherein the first vehicle contains a solution or suspension of the coating material and the second vehicle contains a dispersion of the substrate.

94. A method according to claim 93 wherein the first and second vehicles and supercritical fluid are introduced separately into the vessel.

95. A method according to claim 93 wherein said substrate comprises a pharmaceutically active agent.

96. A method according to claim 93 wherein said substrate comprises a pharmaceutically acceptable carrier.

97. A method according to claim 96 wherein said coating material comprises a pharmaceutically active agent.

98. A method according to claim 95 wherein said coating material comprises a pharmaceutically acceptable carrier.

99. A method according to claim 98 wherein said carrier comprises a taste-masking agent.

100. A method for forming particulates comprising a substrate surrounded by a coating layer comprising:

controlling the temperature and pressure within a particle formation vessel; and
contacting a first vehicle containing a coating material and a second vehicle containing a substrate with a supercritical fluid upon co-introduction into the particle formation vessel such that the flow of supercritical fluid can simultaneously extract the first and second vehicles.

101. A method according to claim 100 wherein said first vehicle contains a solution or suspension of the coating material and the second vehicle contains a dispersion of the substrate.

102. A method according to claim 101 wherein said substrate comprises a pharmaceutically active agent.

103. A method according to claim 101 wherein said substrate comprises a pharmaceutically acceptable carrier.

104. A method according to claim 103 wherein said coating material comprises a pharmaceutically active agent.

105. A method according to claim 102 wherein said coating material comprises a pharmaceutically acceptable carrier.
106. A method according to claim 105 wherein said carrier comprises a taste-masking agent.
107. A method for separating isomers comprising:
contacting a mixture of isomers in a first vehicle with a supercritical fluid upon co-introduction into a particle formation vessel.
108. A method according to claim 107 wherein the isomer mixture and supercritical fluid are co-introduced such that the flow of supercritical fluid can simultaneously extract the first vehicle.
109. Method according to claim 107 further comprising controlling the temperature and pressure within the particle formation vessel.
110. Method according to claim 107, wherein the co-introduction of the supercritical fluid and the vehicle is effected using a coaxial nozzle the outlet end of which communicates with the interior of the particle formation vessel, the nozzle having coaxial passages which terminate adjacent to one another at the outlet end, at least one of the passages serving to carry a flow of the supercritical fluid, and at least one of the passages serving to carry a flow of the vehicle.
111. Method according to claim 110, wherein the pressure in the particle formation vessel is maintained substantially in excess of the critical pressure for the supercritical fluid, whilst the temperature in the vessel is maintained at slightly above the critical temperature for the supercritical fluid.
112. Method according to claim 107, wherein the ratio of the vehicle flow rate to the supercritical fluid flow rate is between 0.001 and 0.1.

113. Method according to claim 107 further comprising co-introducing a second vehicle

114. A product made by the process of any one of claims 45-47, 52-55, 57-66, 70-76,
80-82, 87, 88, 90, 100 or 107-113.

115. A product according to claim 114 in a single polymorphic form.

116. A product according to claim 114 in a single isomeric form.

117. A product according to claim 114 comprising a multi-component particulate.

118. A product according to claim 114 comprising a protein.

119. A product according to claim 114 comprising a sugar.

120. A product according to claim 114 in amorphous form.

121. A product according to claim 114 comprising a substrate provided with a coating.

122. A product according to claim 114 in crystalline form

123. A method according to any one of claims 115-122 further comprising administering the particulates by inhalation.

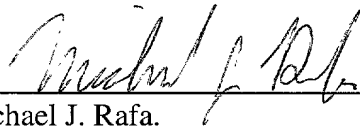
CONCLUSION

Attached hereto is a marked-up version of the changes made to the title and claims by the current amendment. The attached page is captioned **“Version with markings to show changes made.”**

Applicants believe that all the pending claims are presently in condition for allowance. However, the Examiner is invited to telephone the undersigned attorney at the number below if it is believed that this will expedite prosecution of the present application.

Respectfully submitted,

Dated: 11/27/01

By: 
Michael J. Rafa.
Registration No. 38,740
Attorney of Record

(650) 631-5053

“Version with markings to show changes made.”

In the specification:

The paragraph at page 1, line 4 is new.

Claims 1-29 have been cancelled.

Claims 30-123 are new.

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